The rejection objects to the term "prodrugs" in the claims and asserts that the specification does not describe how to make or use such prodrugs sufficiently to enable one skilled in the art to do so. The comments in the Office Action indicate a clear misunderstanding of the nature of the claimed invention. The inventors are not claiming to have invented any new prodrugs. Nor are they claiming any way of making any new prodrugs. Prodrugs of the anthracyclines and mitoxantrone and the ways of making and using them are well known to persons skilled in the art and are considered within the skill of the art. Instead, the invention relates to a method of alleviating problems and difficulties which are known to occur with the use of cardiotoxic medicaments, including already well known and widely used prodrugs of the anthracyclines and mitoxantrone. The rejected claims merely give these compounds as examples of known cardiotoxic medicaments.

As evidence that the anthracyclines, mitoxantrone and prodrugs of these substances are well known to persons skilled in the art, submitted herewith are eight pages of results from a computerized search of the technical literature for relevant published articles. The list commences with four lengthy review articles summarizing the known state of the art relating to anthracycline prodrugs followed by an abstract of an article dealing with prodrugs of mitoxantrone, as well as references to 10 of 28 articles referring to prodrugs of daunorubicin, references to 10 of 77 articles dealing with prodrugs of doxorubicin, references to 10 of 11 articles dealing with prodrugs of adriamycine and references to three

articles dealing with prodrugs of epirubicin. These literature references clearly establish that the prodrugs of the anthracyclines and mitoxantrone are well known to persons skilled in the art.

It is also known in the art that the anthracyclines and mitoxantrone, as well as their known prodrugs, exhibit oxidative-cytotoxic side effects. Importantly, no reason is seen why a person skilled in the art should have any difficulty practicing the claimed invention of alleviating these known side effects by administering an effective side effect inhibiting amount of a compound corresponding to formula I as described and claimed in the instant application. Applicants therefore respectfully submit that their claimed invention is fully enabled to a person skilled in the art, and reconsideration and withdrawal of the rejection are respectfully requested.

In view of the foregoing, all claims of the application are respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this reply or the application in general, a telephone call to the undersigned at (202)624-2845 would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029300.50827US).

Respectfully submitted,

December 2, 2004

J. D. Evans
Registration No. 26,269

Attachment: Literature Search Results (8 pages)

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:sjm

Prodrugs: Anthracyclines, MITOXANTRONE, DAUNORUBICIN, DOXORUBICIN, ADRIAMYCIN, EPIRUBICIN

In Literature

1) Reviews:

L12 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:298570 HCAPLUS
DN 141:324942
TI **Enzyme-catalyzed activation of anticancer prodrugs**
AU Rooseboom, Martijn; Commandeur, Jan N. M.; Vermeulen, Nico P. E.
CS Leiden/Amsterdam Center for Drug Research (L.A.C.D.R.), Division of Molecular Toxicology, Department of Pharmacochemistry, Vrije Universiteit Amsterdam, Amsterdam, 1083, Neth.
SO **Pharmacological Reviews** (2004), 56(1), 53-102
CODEN: PAREAQ; ISSN: 0031-6997
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal; ***General Review***
LA ***English***
AB **A review.** The rationale for the development of **prodrugs** relies upon delivery of higher concns. of a drug to target cells compared to administration of the drug itself. In the last decades, numerous **prodrugs** that are enzymically activated into anticancer agents have been developed. This review describes the most important enzymes involved in **prodrug** activation notably with respect to tissue distribution, up-regulation in tumor cells and turnover rates. The following endogenous enzymes are discussed: aldehyde oxidase, amino acid oxidase, cytochrome P 450 reductase, DT-diaphorase, cytochrome P 450, tyrosinase, thymidylate synthase, thymidine phosphorylase, glutathione S-transferase, deoxycytidine kinase, carboxylesterase, alk. phosphatase, .beta.-glucuronidase and cysteine conjugate .beta.-lyase. In relation to each of these enzymes, several **prodrugs** are discussed regarding organ- or tumor-selective activation of clin. relevant **prodrugs** of 5-fluorouracil, axazaphosphorines (cyclophosphamide, ifosfamide, and trofosfamide), paclitaxel, etoposide, **anthracyclines** (**doxorubicin**, **daunorubicin**, **epirubicin**), mercaptopurine, thioguanine, cisplatin, melphalan, and other important **prodrugs** such as menadione, mitomycin C, tirapazamine, 5-(aziridin-1-yl)-2,4-dinitrobenzamide, ganciclovir, irinotecan, dacarbazine, and amifostine. In addn. to endogenous enzymes, a no. of nonendogenous enzymes, used in antibody-, gene-, and virus-directed enzyme **prodrug** therapies, are described. It is concluded that the development of **prodrugs** has been relatively successful; however, all **prodrugs** lack a complete selectivity. Therefore, more work is needed to explore the differences between tumor and nontumor cells and to develop optimal substrates in terms of substrate affinity and enzyme turnover rates for **prodrug**-activating enzymes resulting in more rapid and selective cleavage of the **prodrug** inside the tumor cells.
CC 1-0 (Pharmacology)
IT ***Anthracyclines***
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(***prodrug*** of ***anthracycline*** were enzymically activated using endogenous and nonendogenous enzymes and development of ***prodrugs*** has been successful but with lack of complete

selectivity)
IT ***20830-81-3*** , **Daunorubicin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(***prodrug*** of ***anthracycline*** that include **daunorubicin** was enzymically activated using endogenous and nonendogenous enzymes and development of ***prodrugs*** has been successful but with lack of complete selectivity)
IT ***23214-92-8*** , **Doxorubicin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(***prodrug*** of ***anthracycline*** that include **doxorubicin** was enzymically activated using endogenous and nonendogenous enzymes and development of ***prodrugs*** has been successful but with lack of complete selectivity)
IT ***56420-45-2*** , **Epirubicin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(***prodrug*** of ***anthracycline*** that include **epirubicin** was enzymically activated using endogenous and nonendogenous enzymes and development of ***prodrugs*** has been successful but with lack of complete selectivity)
RE.CNT 337 THERE ARE 337 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:824354 HCAPLUS
DN 140:174228
TI **Selective activation of anthracycline prodrugs for use in conjunction with ADEPT**
AU HariKrishna, D.; Rao, A. Raghu Ram; Krishna, D. R.
CS Department of Medicinal Chemistry, Kakatiya University, Warangal, 506 009, India
SO **Drug News & Perspectives** (2003), 16(5), 309-318
CODEN: DNPEED; ISSN: 0214-0934
PB Prous Science
DT Journal; ***General Review***
LA ***English***
AB **A review**. A major limitation in the chemotherapy of cancer results from the lack of tumor specificity displayed by most anticancer drugs. In this regard, a great deal of research has been focused on the development of new chemotherapeutic agents that are able to effectively exploit the differences between neoplastic and normal tissues. Several cancerous tissues and tumors are rich in certain lysosomal enzymes as compared with those found in the normal tissues. Thus, a **prodrug** can be designed to selectively target such tumor cells where it can be activated to antineoplastic agent by tumor-assocd. antigen-targeted monoclonal antibody-enzyme conjugate (antibody directed enzyme **prodrug** therapy (ADEPT) strategy) or by the action of an enzyme present at high levels in tumor tissues (**prodrug** monotherapy strategy). This approach protects the normal cells from the cytotoxic effects of the drug. In the last few years, a no. of new MAb-based reagents has been clin. approved (Rituxan, Herceptin and Panorex), and several others are now in advanced clin. trials. This review focuses on the design of several different enzyme/**prodrug** combinations with an emphasis on mechanistic insight and clin. activity.
CC 1-0 (Pharmacology)
Section cross-reference(s): 63
IT Antitumor agents
Human
(antitumor ***anthracycline*** ***prodrug*** selective

activation for use in conjunction with antibody-directed enzyme ***prodrug*** therapy)

IT ***Anthracyclines***
Enzymes, biological studies
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor ***anthracycline*** ***prodrug*** selective activation for use in conjunction with antibody-directed enzyme ***prodrug*** therapy)

IT Antibodies and Immunoglobulins
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; antitumor ***anthracycline*** ***prodrug*** selective activation for use in conjunction with antibody-directed enzyme ***prodrug*** therapy)

IT Drug delivery systems
(***prodrugs*** ; antitumor ***anthracycline*** ***prodrug*** selective activation for use in conjunction with antibody-directed enzyme ***prodrug*** therapy)

RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:263606 HCAPLUS
DN 135:70474
TI Novel **anthracycline prodrugs**
AU Damen, Eric W. P.; De Groot, Franciscus M. H.; Scheeren, Hans W.
CS Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Nijmegen, 6525 ED, Neth.
SO **Expert Opinion on Therapeutic Patents** (2001), 11(4), 651-666
CODEN: EOTPEG; ISSN: 1354-3776
PB Ashley Publications Ltd.
DT Journal; ***General Review***
LA ***English***
AB A review with 92 refs. This paper highlights recent patents in the field of **anthracycline prodrugs**, which are employed in tumor-selective chemotherapy. The **prodrugs** can be a part of a two-step directed enzyme **prodrug** therapy (DEPT), which involves the localization of the prodrug trigger at the tumor site, followed by the administration of the **prodrug** and subsequent tumor-selective **anthracycline** release. In most cases this trigger is an enzyme, which is indirectly localized by an antibody (ADEPT) or a gene encoding for an enzyme (GDEPT). Furthermore, **anthracyclines** can be targeted to the tumor site via **prodrug** monotherapy. **Anthracycline prodrugs** exploiting differences in physiol. conditions, such as a lower pH and a lower oxygen tension in tumor tissue compared to healthy tissue, tumor-specific enzymes, such as plasmin, cathepsin B and .beta.-glucuronidase are discussed. Finally, **prodrugs** are reviewed that home to tumor-selective receptors. Promising advances in this field concern receptors that are required for angiogenesis.
CC 1-0 (Pharmacology)
IT Antitumor agents
(novel ***anthracycline*** ***prodrugs***)

IT ***Anthracyclines***
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel ***anthracycline*** ***prodrugs***)

IT Drug delivery systems

(***prodrugs*** ; novel ***anthracycline*** ***prodrugs***)

IT Angiogenesis
(receptors required for; novel ***anthracycline*** ***prodrugs***)

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:308690 HCAPLUS
DN 133:135474
TI **Prodrugs of natural anthracyclines suited for antibody directed enzyme prodrug therapy (ADEPT) and prodrug monotherapy (PMT)**
AU Michel, S.; Desbene, S.; Gesson, J.-P.; Monneret, C.; Tillequin, F.
CS Laboratorie de Pharmacognosie, U.R.A. au C.N.R.S. N 1310, Paris, 75270, Fr.
SO Studies in Natural Products Chemistry (2000), 21(Bioactive Natural Products (Part B)), 157-180
CODEN: SNPCE2
PB Elsevier Science B.V.
DT Journal; ***General Review***
LA ***English***
AB **A review with 76 refs.** The chem. efficacy of most anticancer agents, including **anthracyclines** such as **daunorubicin** and **doxorubicin**, is severely hampered by general toxicity and by the appearance of acquired resistance. The Antibody Directed-Enzyme **Prodrug** Therapy (ADEPT) concept aims at modifying the distribution of such drugs. It entails the use of an enzyme-antibody conjugate targeted towards the tumor cell surface, in conjunction with a non-cytotoxic **prodrug**, which can be converted upon enzyme activation, into the cytotoxic species. By this way, high local concn. of drug can be specifically obtained at the tumor site, resulting in decreased general toxicity, when compared with classical chemotherapy. We report here the synthesis and biol. behavior of triparte **prodrugs** in which an osidic specifier is linked to the primary amino function of an thracycline through a self-immolative ortho- or para-hydroxybenzyl connector. This spacer can undergo spontaneous 1,4- or 1,6-elimination, after enzymic cleavage of the specifier, to generate the free **anthracycline**. Para-hydroxybenzyl glucuronic **prodrugs** of **doxorubicin**, exhibited strongly reduced cytotoxicity when compared to the parent drug and efficiently released **doxorubicin** upon cleavage by a fusion protein consisting of the humanized anti-carcinoembryogenic monoclonal antibody and of the non-circulating human .beta.-D-glucuronidase. Injection of **prodrug** alone into animals bearing necrotic tumors resulted in therapeutic effects superior to conventional chemotherapy, as a consequence of selective activation by .beta.-D-glucuronidase liberated in necrotic areas. This latter observation recently led to the new concept of **prodrug** monotherapy (PMT).
CC 33-0 (Carbohydrates)
Section cross-reference(s): 1, 7, 63
IT Antibodies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoclonal; ***prodrugs*** of natural ***anthracyclines*** suited for antibody directed enzyme ***prodrug*** therapy (ADEPT) and ***prodrug*** monotherapy (PMT))
IT Antitumor agents
Chemotherapy
Cytotoxic agents
Cytotoxicity

Therapy
(***prodrugs*** of natural ***anthracyclines*** suited for antibody directed enzyme ***prodrug*** therapy (ADEPT) and ***prodrug*** monotherapy (PMT))

IT ***Anthracyclines***
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(***prodrugs*** of natural ***anthracyclines*** suited for antibody directed enzyme ***prodrug*** therapy (ADEPT) and ***prodrug*** monotherapy (PMT))

IT Drug delivery systems
(***prodrugs*** ; ***prodrugs*** of natural ***anthracyclines*** suited for antibody directed enzyme ***prodrug*** therapy (ADEPT) and ***prodrug*** monotherapy (PMT))

RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

---

2) Citations and Titles: individual Substances

A) MITOXANTRON

L14 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:638252 HCAPLUS
DN 121:238252
TI **Incorporation of lipophilic ***prodrugs*** of ametantrone and mitoxantrone inside low density lipoproteins (LDL) and selective uptake of the ***prodrug*** LDL complex via the LDL receptor pathway**
AU Monard-Herkt, F.; Teissier-Morier, E.; Favre, G.; Samadi-Baboli, M.; Soula, G.; Houssin, R.; Bernier, J. L.; Henichart, J. P.; Martin-Nizard, F.; et al.
CS Pasteur Institute, Lille, Fr.
SO **Acta Therapeutica** (1993), 19(4), 317-35
CODEN: ACTTDZ; ISSN: 0378-0619
DT ***Journal***
LA English
AB Low-d. lipoprotein (LDL) particles are potential drug carriers, but only lipophilic drug species partition into the core of the system. In this study, ametantrone (AQ) and **mitoxantron**e (DHAQ) have been coupled to different fatty acids (stearate, palmitate, oleate, linolenate). The linolenate esters of AQ and DHAQ incorporate in highest concn. into LDL using the following protocol of incubation. The **prodrug** (dilinolenate of DHAQ) was dissolved in Intralipid (a parental triglyceride rich emulsion) and then incubated with LDL and lipoprotein deficient serum or albumin for 18 h at 37.degree.C. This method provides substantial incorporation of dilinolenate-DHAQ into LDL (26 mols. of dilinolenate-DHAQ per LDL particle). The dilinolenate-DHAQ-LDL complex was recognized by apolipoprotein B and E receptors, in vitro and in vivo in the rabbit. The pharmacol. efficiency of both free dilinolenate-DHAQ and dilinolenate-DHAQ-LDL complex was 1000 times less cytotoxic on A 549, A 431 and L 1210 cells than free DHAQ. We conclude that this method of incorporation allows the incorporation of a consistent concn. of **prodrug** inside LDL and prevents aggregation of the lipoprotein during the prepn. of the **prodrug**-LDL complex. This complex is incorporated into the cell both in vitro and in vivo via the LDL receptor pathway.
CC 63-5 (Pharmaceuticals)

IT 158439-18-0P 158439-19-1P 158439-20-4P 158439-21-5P 158439-22-6P
158439-23-7P 158439-24-8P 158439-25-9P ***158439-26-0P***
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(incorporation of lipophilic ***prodrugs*** of ametantrone and **mitoxantrone** inside low d. lipoproteins)
IT 64862-96-0D, Ametantrone, fatty acid esters ***65271-80-9D*** ,
Mitoxantrone, fatty acid esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(incorporation of lipophilic ***prodrugs*** of ametantrone and **mitoxantrone** inside low d. lipoproteins)

B) DAUNORUBICIN

Wenn Du zugehörige Abstracts haben möchten, bitte melden!

L15 ANSWER 1 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Extracellular .beta.-glucuronidase for gene-directed enzyme-***prodrug*** therapy

L15 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Cytosolic .beta.-glycosidases for activation of glycoside ***prodrugs*** of **daunorubicin**

L15 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Enzyme-activated ***prodrug*** therapy enhances tumor-specific replication of adenovirus vectors

L15 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI PDEPT: polymer-directed enzyme ***prodrug*** therapy. I. HPMA copolymer-cathepsin B and PK1 as a model combination

L15 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Drug delivery systems based on trimethyl lock lactonization: Poly(ethyleneglycol) ***prodrugs*** of amino-containing compounds

L15 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Melanocyte-Directed enzyme ***prodrug*** therapy (MDEPT). Development of second generation ***prodrugs*** for targeted treatment of malignant melanoma

L15 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI A **daunorubicin** .beta.-galactoside ***prodrug*** for use in conjunction with gene directed enzyme ***prodrug*** therapy

L15 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Intensely cytotoxic **anthracycline** ***prodrugs*** : galactosides

L15 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Drug Delivery Systems Based on Trimethyl Lock Lactonization: Poly(ethylene glycol) ***Prodrugs*** of Amino-Containing Compounds

L15 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Synthesis and Biological Evaluation of Novel ***Prodrugs*** of **Anthracyclines** for Selective Activation by the Tumor-Associated Protease Plasmin

C) DOXORUBICIN

L16 ANSWER 1 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI LEAPT: Lectin-directed enzyme-activated ***prodrug*** therapy

L16 ANSWER 2 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Engineering a thermostable human prolyl endopeptidase for antibody-directed enzyme ***prodrug*** therapy

L16 ANSWER 3 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI ***Prodrug*** chemotherapeutics bypass p-glycoprotein resistance and kill tumors in vivo with high efficacy and target-dependent selectivity

L16 ANSWER 4 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Plasmin-activated **doxorubicin** ***prodrugs*** containing a spacer reduce tumor growth and angiogenesis without systemic toxicity

L16 ANSWER 5 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Pronounced Antitumor Efficacy by Extracellular Activation of a **Doxorubicin**-Glucuronide ***Prodrug*** After Adenoviral Vector-Mediated Expression of a Human Antibody-Enzyme Fusion Protein

L16 ANSWER 6 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI **Doxorubicin** ***prodrug*** on the basis of tert-butyl cephalosporanate sulfones

L16 ANSWER 7 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Bioactivation of Self-Immolative Dendritic ***Prodrugs*** by Catalytic Antibody 38C2

L16 ANSWER 8 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Extracellular .beta.-glucuronidase for gene-directed enzyme-***prodrug*** therapy

L16 ANSWER 9 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI A New Aliphatic Amino ***Prodrug*** System for the Delivery of Small Molecules and Proteins Utilizing Novel PEG Derivatives

L16 ANSWER 10 OF 77 HCAPLUS COPYRIGHT 2004 ACS on STN
TI HPLC-MS/MS determination of a peptide conjugate ***prodrug*** of **doxorubicin**, and its active metabolites, leucine-doxorubicin and **doxorubicin**, in dog and rat plasma

D) ADRIAMYCIN

L17 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI A New Aliphatic Amino ***Prodrug*** System for the Delivery of Small Molecules and Proteins Utilizing Novel PEG Derivatives

L17 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Enhanced antitumor efficacy of an albumin-binding **doxorubicin** ***prodrug*** designed to be cleaved by matrix metalloproteinase 2

L17 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Overexpression of Legumain in Tumors Is Significant for

Invasion/Metastasis and a Candidate Enzymatic Target for ***Prodrug*** Therapy

L17 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Activation of Adriamycin by the pH-dependent Formaldehyde-releasing ***Prodrug*** Hexamethylenetetramine

L17 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Molecular basis for the synergistic interaction of adriamycin with the formaldehyde-releasing ***prodrug*** pivaloyloxymethyl butyrate (AN-9)

L17 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Elongated Multiple Electronic Cascade and Cyclization Spacer Systems in Activatible Anticancer ***Prodrugs*** for Enhanced Drug Release

L17 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Synthesis and Biological Evaluation of Novel ***Prodrugs*** of **Anthracyclines** for Selective Activation by the Tumor-Associated Protease Plasmin

L17 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Intensely Cytotoxic **Anthracycline** ***Prodrugs*** : Glucuronides

L17 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Monomethoxytrityl (MMT) as a versatile amino protecting group for complex ***prodrugs*** of anticancer compounds sensitive to strong acids, bases and nucleophiles

L17 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Targeting of macromolecular ***prodrug*** to T-lymphocytes

E) EPIRUBICIN

L18 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Extracellular .beta.-glucuronidase for gene-directed enzyme-***prodrug*** therapy

L18 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Simultaneous high-performance liquid chromatographic determination of a glucuronyl ***prodrug*** of **doxorubicin**, doxorubicin and its metabolites in human lung tissue

L18 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
TI A new application for liposomes in cancer therapy. Immunoliposomes bearing enzymes (immuno-enzymosomes) for site-specific activation of ***prodrugs***